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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/828,623	04/21/2004	Daniel B. Carr	2004117-0008 (NEMC 197-DI	5207

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EXAMINER	
LANDSMAN, ROBERT S	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 09/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/828,623	CARR ET AL.	
	Examiner	Art Unit	
	Robert Landsman	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-42* is/are pending in the application.

4a) Of the above claim(s) *39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) ~~24-42~~ 24-38, 40-42 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/7/06; 4/21/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Formal Matters

A. The Amendment filed 8/21/06 has been entered into the record.

B. Claims 24-42 are pending. Claim 39 has been withdrawn as being drawn to a non-elected invention. Therefore, claims 24-38 and 40-42 are the subject of this Office Action. Since Applicants did not provide a traversal, the Election is treated as one without traverse. Therefore, the Restriction is deemed proper and is, therefore, made FINAL. It is noted, however, that Applicants have referred to the Restriction as an election of species. It is not. The sequences are independent and distinct for the reasons provided in the Restriction. However, reconsideration of the non-elected sequences and claims will be considered if the claims are found allowable.

C. The Information Disclosure Statement filed 3/7/06 has been entered into the record.

D. The Information Disclosure Statement filed 4/21/04 has been entered into the record.

2. Oath

The oath or declaration is missing. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

3. Specification

A. The specification is objected to since there is a typographical error on page 3, line 4. the word "intracerebrpvertricularly," which is circled, has an extra "l."

B. According to 37 CFR 1.821(d) (MPEP § 2422), where the description or claims of a patent application discuss a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the assigned identifier, in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application. A sequence appears in Table 4 on page 17 of the specification ("ethyl ester"), but is not identified by SEQ ID NO as required.

4. Claim Objections

A. Claims 29, 31, 36 and 39 are objected to since they recite non-elected subject matter (SEQ ID NO:s). Applicants are not required to cancel this subject matter. This issue can be handled if the present invention is found allowable.

5. Claim Rejections - 35 USC § 112, first paragraph – scope of enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

A. Claim 40 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while then being enabling for methods of administering the chimeric peptide i.v or systemically, does not reasonably provide enablement for methods of administering the protein i.c.v. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims read on treating humans. However, the specification provides no guidance or working examples of methods of administering compounds i.c.v. to humans. Furthermore, it is not predictable to one of ordinary skill in the art how to safely and effectively administer these peptides i.c.v. to a human, leading the Examiner to hold that undue experimentation is necessary to practice the invention as claimed.

6. Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

A. Claims 24-28 and 32-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lipkowski et al. (Life Sci. 33:141-144, 1983 – on Form PTO-1449 filed 4/21/04). The claims are drawn to a method of treating pain in a mammal by administering a chimeric peptide comprising an N-terminal opioid receptor binding moiety and a C-terminal Substance P receptor agonist binding moiety.

Lipkowski et al. (Life Sci.) teach chimeras in which the N-terminal part of the SP receptor agonist binding moiety, SP, was replaced by an enkephalin (opioid receptor binding moiety) active fragment, which comprises Tyr^1 – Phe^4, and that this peptide demonstrated naloxone-reversible opiate activity in various in vivo tests (Abstract and Figure 1). Lipkowski et al. also teach that most endogenous opioid peptide analogs, such as endomorphin 1 and endomorphin 2, contain an N-terminal tetrapeptide fragment and that this tetrapeptide, Tyr^1 – Phe^4, is an important requirement for opioid activity (first paragraph of the Introduction). Though enkephalin is more specific to delta-opioid receptors, it still meets the limitation of claim 26 since, due to the fact that ligands do not only bind to one receptor, enkephalin would be expected to bind to the mu-opioid receptor.

Lipkowski do not specifically teach the use of these compounds to treat pain in a mammal. However, it would have been obvious to one of ordinary skill in the art at the time of the present invention to have treated mammals with these compounds since it was well-known at the time that opioids inhibit pain. Therefore, the artisan would have been motivated to use these compounds to inhibit pain in mammals.

B. Claims 24-38 and 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lipkowski et al. (Life Sci. 33:141-144, 1983 – on Form PTO-1449 filed 4/21/04) in view of Lipkowski et al. (in β-Casomorphins and Related Peptides: Recent Developments, p 113-118, 1994 – on Form PTO-1449 filed 4/21/04) further in view of and further in view of Maszczynska et al. (Let. Pep. Sci. 5:395-398, 1998).

The claims and the teachings of Lipkowski et al. (Life Sci.) are discussed above. However, Lipkowski et al. (Life Sci.) do not teach the specifically claimed SEQ ID NOs. However, Lipkowski et al. (in β-Casomorphins...) teach the production of a chimeric peptide comprising the N-terminal fragment of a casomorphin, Tyr-Pro-D-Phe-Phe, (an opioid binding moiety. Table 1 of the specification) with the C-terminal fragment of an SP antagonist, to produce the chimera, Tyr-Pro-D-Phe-Phe-D-Phe-D-Trp-Met-NH_2 (Abstract). This N-terminal fragment of casomorphin comprises an N-terminal Tyr (free amine), and this "Tyr-Pro-Phe-Phe" tetrapeptide agonist (i.e. ligand) is 100% identical to that of SEQ ID NO:3 of the

present invention, except for the substitution of the "D-amino acid," D-Phe. Lipkowski (in β-Casomorphins...) also teach the Substance P receptor agonist binding moiety, SP, which is 100% identical to SEQ ID NO:21 of the present invention, and that the amidated (i.e. protected, Met-NH_2) C-terminal fragment of the agonist, SP, itself, Phe-Phe-Gly-Leu-Met-NH_2, is biologically active (Figures 1 and 2) in producing contractions in the guinea pig ileum. Lipkowski et al. (in β-Casomorphins...) also teach pharmaceutically acceptable diluent (i.e. NaCl; Figure 3; page 114, paragraphs 1 and 3 under "Materials and Methods").

It would have been obvious to one of ordinary skill in the art at the time of the invention to have produced peptide chimeras comprising the N-terminus of any mu opioid receptor binding moieties which comprises the tetrapeptide, Tyr^1 – Phe^4, including endomorphin 1 or endomorphin 2 (SEQ ID NO:3 of the present invention), and the C-terminus of an SP receptor agonist binding moiety (i.e. a C-terminal fragment of SEQ ID NO:21 of the claimed invention). One of ordinary skill in the art would have been motivated to combine the teachings of Lipkowski et al. (in β-Casomorphins...) and Lipkowski et al. (Life Sci.) in view of Maszczynska et al. (Let. Pep. Sci.) who teach that SP is capable of reinforcing spinal morphine (a mu opioid agonist binding moiety) analgesia as seen in the tail-flick test (Abstract; page 396, left column, first full paragraph). This pharmacological effect was blocked by administration of naloxone, demonstrating that this potentiated analgesic effect is mediated by activation of opioid expressing neurons. Maszczynska et al. (Let. Pep. Sci.) also teach that findings of SP reinforcement of morphine analgesia indicates the complementary, and potential value, of further attention to combination pharmacotherapies applying SP and opioids in concert (Conclusion).

One of ordinary skill in the art would have also had a reasonable expectation of success in producing chimeras comprising the N-terminus of an OM and the C-terminus of an SPM since techniques to produce chimeras were well-known and highly successful in the art at the time of the present invention, as evident from the above teachings by both Lipkowski et al. (in β-Casomorphins...) and Lipkowski et al. (Life Sci.) who teach that OM/SPM peptide chimeras already exist and that these chimeras are capable of acting via opioid receptor-expressing neurons to potentiate opioid analgesia.

Finally, the use of opioid drugs, including opioid peptides, has been accompanied by side-effects such as dependence, tolerance and respiratory depression (Lipkowski et al. in β-Casomorphins and Related Peptides: Recent Developments). Therefore, to limit the potential side-effects of opioid drugs, and to stimulate "as many receptors involved in pain transmission and modulation as possible," chimeras between opioids and non-opioid peptides should be considered in the search for potential analgesic drugs (page 114, last paragraph of Introduction). These combined teachings will allow the artisan to further

elucidate the mechanism of action of both the opioid and SP receptor systems, as well as to identify and use other OM/SPM chimeras for the induction of analgesia, as taught in the prior art.

7. Conclusion

A. No claim is allowable.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (571) 272-0888. The examiner can normally be reached on M-Th 10 AM – 7 PM (eastern).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert Landsman
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Art Unit 1647